Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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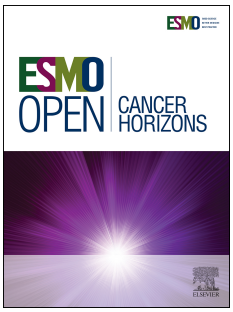

COVID-19 in patients with cancer: first report of the ESMO international, registry-based, cohort study (ESMO CoCARE)

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COVID-19 in patients with cancer: first report of the ESMO international, registry-based, cohort study (ESMO CoCARE)

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Abbreviations (by order of appearance):

OS - Overall survival; SARS-CoV-2 - Severe acute respiratory syndrome coronavirus-2; ESMO-CoCARE - ESMO COVID-19 and CAncer Registry; REDCap - Research Electronic Data Capture; CHUV - Centre Hospitalier Universitaire Vaudois; WHO - World Health Organization; PS-Performance status; NLR - Neutrophil-lymphocyte ratio; PLR - Platelet-lymphocyte ratio; OIS - OnCovid inflammatory score; NED - no evidence of malignant disease; eCRF - electronic case report form;

Abstract

Background

ESMO-CoCARE is an international collaborative registry-based, cohort study, gathering real-world data from Europe, Asia/Oceania and Africa on the natural history, management and outcomes of patients with cancer infected with SARS-CoV-2.

Methods

ESMO-CoCARE captures information on patients with solid/haematological malignancies, diagnosed with COVID-19. Data collected since 06/2020 include demographics, co-morbidities, laboratory measurements, cancer characteristics, COVID-19 clinical features, management and outcome. Parameters influencing COVID-19 severity/recovery were investigated as well as factors associated with overall survival (OS) upon SARS-CoV-2 infection.

Results

This analysis includes 1626 patients from 20 countries (87% from 24 European, 7% from 5 Northern African, 6% from 8 Asian/Oceanian centers), with COVID-19 diagnosis from January 2020 up to May 2021. Median age was 64 years, with 52% female, 57% cancer stage III/IV and 65% receiving active cancer treatment. 64% patients required hospitalization due to COVID-19 diagnosis, with 11% receiving intensive care. In multivariable analysis, male gender, older age, ECOG PS≥2, BMI<25, presence of co-morbidities, symptomatic disease, as well as haematological malignancies , active/progressive cancer , neutrophil-lymphocyte ratio ≥ 6 and OnCovid inflammatory score (OIS) ≤ 40 were associated with COVID-19 severity (i.e., severe/moderate disease requiring hospitalization). 98% of patients with mild COVID-19 recovered, as opposed to 71% with severe/moderate disease. Advanced cancer stage was an additional adverse prognostic factor for recovery. At data cut-off, and with median follow-up of 3 months, the COVID-19-related death rate was 24.5% (297/1212), with 380 deaths recorded in total. Almost all factors associated with COVID-19 severity, except for BMI and NLR, were also predictive of inferior OS, along with smoking and non-Asian ethnicity.

Conclusions

Selected patient and cancer characteristics related to gender, ethnicity, poor fitness, comorbidities, inflammation, and active malignancy predict for severe/moderate disease and adverse outcomes from COVID-19 in patients with cancer.

Keywords: COVID-19; Sars-cov-2; Oncology; Cancer

Highlights:

- ESMO-CoCARE is an international registry on COVID-19 in patients with cancer from centers in Europe, Asia/Oceania and Africa
- Analysis is based on a total of 1626 patients, with 3 months median follow-up
- Overall, 64% had moderate/severe COVID-19 and at data cut-off the COVID-19-related death rate was 25%
- Risk factors for COVID-19 severity included patient and cancer-related characteristics, and systemic inflammation
- Our data add evidence to support clinicians and regulatory bodies for the management of COVID-19 in patients with cancer

Introduction

In the beginning of 2020, a striking increase in cases and deaths from a new virus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and its disease (COVID-19), startled the worldwide community. Clinical features associated with COVID-19 included fever, fatigue, dry cough, acute respiratory distress syndrome, blood test abnormalities or ground-glass opacity in the lungs[1, 2]. Additionally, analysis from initial studies identified older age, diabetes, cardiovascular, cerebrovascular and malignant disease as risk factors for COVID-19 severity[1, 2].

Patients with cancer commonly have an immune dysfunction due to the use of immunosuppressive medicines (e.g., cytotoxic drugs, corticosteroids), poor nutritional status or direct effects of the tumour on the fitness of the immune system[3, 4]. They also represent an older population frequently with severe comorbidities. It was, thus, hypothesized that patients with cancer would be at higher risk of experiencing severe COVID-19[3-5]. Rapid changes in cancer care and research were implemented globally[6-8], while screening and diagnostic programmes were severely affected, with subsequent higher prevalence of more advanced-stage presentation [7, 9, 10]. In order to mitigate these evolving issues, several cancer societies developed and regularly updated specific guidelines for cancer care, despite the limited availability of data-driven evidence[11, 12]. An urgent need to study the effects of COVID-19 in patients with cancer emerged and several international groups started to collaborate worldwide, with a swift set-up of dedicated clinically-oriented databases to address this new priority and unmet need[13-15].

Several publications reported on the deleterious effects of COVID-19 in specific cancer patient subgroups[1, 2, 16-18]; however, the heterogeneous data collection and lack of statistical power were important limitations leading, in some cases, to contradictory results[17]. It became, therefore, essential to gather larger and more robust datasets powered to study the effects of COVID-19 in different subgroups of patients with cancer (i.e.: histology, staging, treatments) from various geographic areas.

The ESMO COVID-19 and CAncer REgistry (ESMO-CoCARE) was initiated to meet this goal and was designed as a large, observational multicenter, transnational database, including centers from Europe, Africa, and Asia/Oceania in order to study the effects of COVID-19 in patients with hematologic or solid tumours[19]. Herein, we present the first ESMO-CoCARE results with data collected until May 2021. We report on risk factors for severity and mortality from COVID-19 in patients with cancer integrating data from centers in Europe, Asia/Oceania, and Africa, and we independently validate observations from similar registries, in an effort to contribute to a better understanding of COVID-19 disease in people with cancer, informing clinicians and regulatory bodies on optimal management.

Methodology

Study design and participants

The ESMO CoCARE is an observational prospective study, based on a longitudinal multicenter survey of patients with cancer with any solid or haematological malignancy that were diagnosed with COVID-19. The data reside in the ESMO CoCARE registry, developed and maintained as an electronic REDCap (Research Electronic Data Capture) database housed at Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland. Active data collection is planned until the end of the pandemic as declared by the World Health Organization (WHO), or the end of epidemic situation in each region, with subsequent follow-up as needed.

Data on clinical features, course of the disease, management and outcomes are collected for both cancer and COVID-19 disease. The aim of the study is primarily descriptive of the characteristics of COVID-19 in patients with cancer, exploring associations with both cancer and COVID-19 outcomes. Data reported here were extracted from medical records of consecutive patients diagnosed with COVID-19 from 1st-January-2020 up to 18th-May-2021. COVID-19 diagnosis included both laboratory-confirmed COVID-19 cases (irrespective of symptoms and clinical presentation) and cases with only clinical diagnosis of COVID-19, based on signs such as fever >38^{o}C, cough, diarrhoea, otitis, dysgeusia, anosmia, myalgia, arthralgia, conjunctivitis and rhinorrhoea, lymphocyte count <1.0x10^{9}/L, and/or chest radiographic or lung CT-imaging suggestive of SARS-CoV2-19 pneumonia.

Study objectives and endpoints

The objectives of this study included the identification of risk factors predictive of severity, in terms of hospitalization, or recovery from COVID-19 in patients with cancer, and overall survival. In the current analysis, the following endpoints were considered as co-primary: COVID-19 severity was categorized based on hospitalization requirement and indication for ICU admission (mild: no hospitalization; moderate: hospitalization indicated/took place, without ICU admission; severe: ICU indication/admission). In the univariate/multivariable analyses performed the following grouping was used: moderate/severe, i.e., hospitalization required, versus mild (no hospitalization).

Recovery from COVID-19 illness was defined by the rate of patients with COVID-19 who survived the disease, having a date of recovery reported. Overall survival (OS) was defined as the time from COVID-19 diagnosis until death from any cause. OS was assessed for patients with available follow-up information, i.e., date of death for reported deaths or date of last follow-up for those alive.

Statistical analysis

All the variables of interest were described overall and by the primary outcomes of COVID-19 severity/recovery and OS.

Mann-Whitney and Fisher's exact tests were used for the associations of continuous and categorical variables, respectively, with COVID-19 severity and recovery, while the associations with OS, were explored through log-rank test. Univariable logistic and Cox proportional hazards models were also fitted, for COVID-19 severity/recovery and OS, respectively. Of note, no adjustment of multiple comparisons was performed, and differences are primarily descriptive. Other associations of interest were assessed through Fisher's exact test, e.g., treatment adjustment due to COVID-19 with type of cancer treatment, symptoms and COVID-19 complications with demographics, and others. OS was estimated by the Kaplan-Meier method for the whole analysis cohort with available follow-up information. In the frame of OS analysis, COVID-19 related mortality i.e., deaths reported for patients who did not recover, as well as deaths reported for patients who recovered but died later due to COVID-19 complications, was also assessed.

Multivariable models were also fitted: logistic for COVID-19 severity/recovery and Cox proportional hazards for OS. A pre-selection of baseline variables to be included in the multivariable models was processed to avoid overfitting. Variable selection was based on significance from the univariable analysis ($p<0.10$), clinical relevance, degree of factor missingness, and possible correlation between candidate predictors. Of note, due to the fact that almost all patients who were not hospitalized, finally recovered, multivariable analysis for identifying risk factors for recovery focused only on the hospitalized patients (moderate/severe disease).

The variables initially included were gender, age, ethnicity, ECOG performance status (PS), smoking status, BMI (<25 versus ≥25), co-morbidities, cancer type/stage/status at COVID-19 diagnosis, COVID-19 symptoms (symptomatic/asymptomatic) and the following inflammatory-based biomarkers measured prior to COVID-19 diagnosis: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), OnCovid inflammatory score (OIS). Backward elimination method with removal criterion $p>0.10$ was utilized to obtain the factors with significant effects. Multicollinearity and proportionality assumption based on the Schoenfeld residuals, were checked. Data were analysed using SAS v9.4 and R v4.0.0 software.

Results

Cohort Description and Cancer Disease Characteristics

From January 2020 to May 2021, a total of 1626 eligible patients with COVID-19 diagnosis and a history of active malignancy or in remission, were registered in the CoCARE database and comprised the analysis cohort. COVID-19 was diagnosed most often in March and April 2020 (16.6% and 16.1%, respectively), followed by December 2020 and January 2021 (12.2% and 11.8%, respectively), (Figure S1).

Registration of patients was performed at 37 participating centers in 20 countries, from June 6, 2020, to May 18, 2021. United Kingdom (32%) and Spain (24%) contributed the highest proportion of patients, with 31% from other European countries; 7% and 6% were registered from African and Asian/Oceanian countries, respectively (Table S1, Figure S2).

Cohort demographics, clinical and cancer disease characteristics, are presented in Table 1. Overall, approximately half of the patients were female (52%), with a median age of 64 years, including 563 patients (35%) older than 70 years. Most of the patients were Caucasian (58%). Almost 50% of the patients had ECOG PS=1, while 41% were never smokers. BMI was recorded for 82% of patients, with 547 of them (41%) having BMI<25 (most of whom, 490, with 18.5≤BMI<25), 502 (38%) being overweight (25≤BMI<30) and 280 (21%) obese (≥30).

Regarding clinical characteristics, the majority of the patients had pre-existing co-morbidities (70%), with most common cardiovascular (42%), metabolic (26%) and pulmonary co-morbidities (14%), (Tables 1 & S2a, S2b). Furthermore, almost 60% of the patients received at least one concomitant medication. With respect to cancer disease characteristics, 47% of patients were diagnosed with cancer within the past year. The majority (86%) were solid tumours (breast: 20%, colorectal: 14%, lung: 14%, other: 38%), with haematological malignancies reported only for 9% of the patients. Most of the patients had evidence of active disease at COVID-19 diagnosis (66%), with 21% having no evidence of disease. Over half of the patients had cancer stage III or IV (57%; Table 1).

1053 patients (65%) were receiving anti-cancer treatment. Among them, most were on cytotoxic chemotherapy (69%) or on targeted therapy (15%), (Table S3). For 56% of the patients, the treatment plan was not adjusted due to COVID-19 (Table S3). Treatment adjustment was more often observed for patients on targeted therapy compared to treatments other than targeted (41% vs 29%), and less often for patients on radiotherapy compared to treatments other than radiotherapy (21% vs 32%), (Table S4). Of note, the association of BMI with specific cancer treatments and type/status/stage of cancer was also explored; it was significantly correlated only with cancer type (p=0.0011), with more than 60% of patients with breast or colorectal cancer being overweight/obese (Table S5).

COVID-19 diagnosis and course of illness

Information on COVID-19 diagnosis, course of illness and recovery is provided in Table 2. COVID-19 was confirmed based on laboratory tests for the majority of the patients (76%), including 65% with RT-PCR and 9% with SARS-CoV-2 serologic test.

At initial presentation of COVID-19, 1167 patients (72%) had at least one symptom, with the most frequent being fever (49%), cough (including productive cough) (46%), dyspnea (33%), severe fatigue (21%), myalgia (13%) and headache (11%), (details in Table S6a).

Symptoms were reported more often by older patients, non-Caucasian, of higher ECOG PS, with pre-existing co-morbidities or with lung cancer (Tables S6b-d). Of note, patients with no evidence of malignant disease (NED) appeared more often to be symptomatic compared to those diagnosed in the presence of active cancer disease (87% versus 78%; $p<0.001$; Table S6d). Mild severity of COVID-19 was indicated for 562 patients (36%), moderate for 822 (53%) and severe for 168 (11%), (Table 2).

Complications during COVID-19 illness occurred to 641 patients (39%), most frequently pulmonary (29%), cardiovascular (11%), and systemic (10%), (Table 2). Associations of the most common types of complications with cohort demographics, comorbidities and cancer disease characteristics are provided in Tables S7a-c.

Overall, 609 patients (38%) required supplemental oxygen (Table 2). Treatment for COVID-19 or its sequelae was administered to almost half of the patients (49%), including azithromycin (23%), anticoagulation (23%), hydroxychloroquine (20%) and corticosteroids (16%), (Table S8). Regarding the primary endpoint of recovery, of the 1557 patients with available data, there were 1253 patients (81%) who recovered from COVID-19(Table 2).

Laboratory measurements and inflammatory-based biomarkers

Laboratory measurements were considered at three distinct timepoints: prior to COVID-19 diagnosis; during COVID-19; and at time of recovery, including: white blood cell ($x10^9$/L), neutrophil count ($x10^9$/L), lymphocyte count ($x10^9$/L), platelet count ($x10^9$/L), albumin (g/dL), haemoglobin (mmol/L), creatinine (mg/dL), Na (mmol/L), K (mmol/L) (Figure S3, indicating differences over the different timepoints). CRP values were also collected but not included in the analysis, since many extreme values were reported, casting doubt on their validity.

Measurements prior to COVID-19 formed the basis of primary inference, as measurements at this timepoint were feasible for all patients and could also have predictive significance for the COVID-19 disease. Based on these, additional inflammatory-based biomarkers were calculated, according to the OnCovid dataset[63]. Two OnCovid inflammatory markers involved CRP, and thus are not analysed here. NLR, PLR and OIS, measured prior to COVID-19 for ESMO CoCARE patients, are summarized in Table S9.

COVID-19 severity (hospitalization): Association with baseline factors

The severity rate of COVID-19 (severe/moderate disease, i.e., hospitalization) differentiated significantly according to each of several factors examined (Table S10a). The multivariable model is illustrated in Figure 1a. Severe/moderate COVID-19 disease was experienced more frequently in male patients, patients of older age, with worse ECOG PS (≥2), BMI<25 and a higher number of pre-existing co-morbidities (OR ranged from 1.31 to 2.77). Regarding cancer characteristics, patients with haematological malignancies developed severe/moderate disease more frequently than patients with solid tumours, as well as patients with progressive disease compared to those with no evidence of disease (OR [95%CI]: 1.91 [1.16-3.14] and 1.63 [1.08-2.46], respectively). Symptomatic patients at diagnosis, subsequently developed severe/moderate COVID-19 (OR:10.25 [95%CI: 7.08-14.84]) significantly more often. With respect to inflammatory-based biomarkers, patients with NLR≥6 and patients with OIS≤40 experienced severe/moderate COVID-19 more frequently (OR:2.40 [95%CI:1.56-3.69]), and OR:2.51 [95%CI:1.47-4.30], respectively).

COVID-19 recovery: Association with baseline factors

Recovery from COVID-19 was found to be associated with several risk factors, mostly similar to the ones associated with COVID-19 severity (Table S10a for all patients). In addition, increased recovery rate was found in patients from participating countries in Asia/Oceania, as well as in countries with upper-middle income economies. Among patients with available severity and recovery information, the vast majority (98%) of patients with no need of hospitalization (mild disease) eventually recovered versus a 71% recovery rate among patients with severe/moderate COVID-19 (p<0.001; Table S11). Respective results for the hospitalized patients only are provided in Table S10b.

As illustrated in Figure 1b, in the multivariable analysis, focusing on the group of patients who needed hospitalization, the odds of recovering from COVID-19 disease were lower for male patients (OR:0.52 [95%CI:0.38-0.70]), for older patients (OR:0.84 [95%CI:0.75-0.94]), with worse ECOG PS (≥2) (OR:0.51 [95%CI:0.37-0.71]) and COVID-19 symptoms (OR:0.46 [95%CI:0.23-0.92]). Regarding cancer characteristics, patients with progressive disease compared to patients with no evidence of disease and patients of stage IIII or advanced (IV) compared to patients of stage I/II recovered less often (OR:0.34 [95%CI:0.20-0.59], OR: 0.42 [95%CI: 0.21-0.84] and OR:0.32 [95%CI:0.17-0.61], respectively).

All-cause survival analysis

Based on 1212 patients with follow-up information, the median follow-up time was 3.02 months from COVID-19 diagnosis (IQR:2.96-6.05) with 832 (69%) alive patients at last follow-

up. Overall, a total of 380 (31%) deaths were recorded, with a 1-month OS rate of 78.4% [95%CI:76.0%-80.6%] and a 3-month OS rate of 71.4% [95%CI:68.7%-73.8%]. The median OS time was not reached (Figure 2a). From all patients with available follow-up, a total of 297 deaths were reported as related to COVID-19 complications (24.5%); 256 up to 1-month (97.7% of 262 deaths up to 1-month) and 293 up to 3-months (84.7% of 346 deaths up to that time-point). Hence, from the total of 380 deaths recorded, the majority (78.2%) were attributed to COVID-19 disease, while the remaining 83 deaths were caused by disease progression (12.6%), cancer treatment toxicity (0.3%), other reason (2.1%) or unknown reason (6.8%), (Table S12). As expected, all risk factors significantly associated with COVID-19 recovery, also had a significant impact on OS (Table S10c).

In the final multivariable Cox model, a higher mortality risk was estimated for male gender, older age, Caucasian or other ethnicity as compared to Asian, worse ECOG PS, current/former smoking status and pre-existence of co-morbidities (HR ranged from 1.13 for risk per decade of older age to 3.75 for other versus Asian ethnicity).

Regarding cancer characteristics, mortality risk was higher for haematological malignancies compared to solid tumours (HR:1.54 [95%CI:1.06-2.22]), while an almost three-fold increase in risk was found for progressive disease compared to no evidence of disease (HR:2.78 [95%CI:1.77-4.36]). With respect to inflammatory-based biomarkers, patients with OIS≤40 had a higher risk of death, although only at 10% significance level. Cancer stage at COVID-19 diagnosis and symptoms were included in the model as stratification factors due to detected violation of the proportionality hazard assumption for their effect (explored by the Schoenfeld residuals).

Discussion

Overall, we independently validated previously published observations on variables associated with COVID-19 outcomes in patients with cancer. Additionally, in our study Asian ethnicity and higher BMI (≥25) were associated with better COVID-19 related outcomes. Notably, in multivariable analysis most of the factors affecting severity appeared to have a significant impact on OS at 3 months median follow-up.

The COVID-19-related death in our cohort was 24.5%, which is higher than what has been reported for the general population infected with COVID-19[20-22]. In a retrospective case-control analysis from 15,510 patients, the COVID-19 related death for the overall population was 5.61%, as compared to 14.93% (100/670) in patients with cancer [21]. A meta-analysis from 32 studies and 46,499 patients with COVID-19 (1,776 patients with cancer), demonstrated a higher ICU admission (RR, 1.56; 95% CI, 1.31 to 1.87) and mortality rate (RR, 1.66; 95% CI, 1.33 to 2.07) for patients with cancer comparing to non-cancer population[22]. Interestingly, for

subjects > 65 years old, all-cause mortality was comparable between those with cancer versus without cancer, suggesting the strong effect of age alone for COVID-19 related death[22].

The mortality rate associated with COVID-19 for patients with cancer varies in different studies from 13% to 33.6%[17, 18, 21, 23]. In a systematic review and meta-analysis, including 33,879 patients with cancer and SARS-CoV-2 infection, the overall case-fatality rate was 25.4% (95% CI 22.9%–28.2%), very similar to our findings[24]. In another systematic review and meta-analysis from 17 studies, the pooled in-hospital mortality for the 904 hospitalized patients with COVID-19 and cancer was 14.1%[25].

Those different results might be explained by population heterogeneity and a selection bias towards the most severe cases in some studies. Additionally, a higher mortality rate was reported in the beginning of the pandemic[26-29]. Indeed, in our cohort, 38% of cases were diagnosed between March and May 2020. Moreover, the high proportion of cases with advanced or progressive cancer may have influenced the mortality rate observed.

Older age, male gender, current/former smoking status have been consistently associated with worse COVID-19 related outcomes for the general population, irrespective of a cancer diagnosis[30, 31]. Unsurprisingly similar results were obtained not only in our cohort, but also in other studies in patients with cancer and COVID-19[17, 23, 27, 32]. We were intrigued by a significantly lower mortality for the Asian population in our cohort. During the first wave, the pandemic affected more severely Europe compared to eastern Asia countries[33, 34], reflecting potentially higher social and health system epidemic preparedness in the latter[34]. Importantly, the great majority of the Asian population in our cohort is from Asian cancer centers. Beyond clinical characteristics, it has been hypothesized that host genetics and HLA profiles may influence COVID-19 outcomes[35-39]. Notably, a strong correlation was found between ACE1 II genotype, more frequent in Asians, and lower severity or death from COVID-19[40]. All these factors may justify the favourable survival from COVID-19 observed in our Asian population, which in our best knowledge was not previously reported in other studies on patients with cancer[21, 28, 41]. Nevertheless, considering the low sample size (117 Asians out of 1626 patients), further confirmative analysis in larger populations is needed.

Moreover, in our study other ethnicities (mainly reported from European centers) tend to have higher, but not statistically significant, mortality rate compared to Caucasians. It has been consistently demonstrated that ethnic minorities in Europe and North America have been more severely affected by COVID-19[42-46], including patients with cancer[21, 28]. Social determinants of health, including poorer socioeconomic status, adverse working conditions, decreased access to healthcare or social exclusion may have contributed to these findings[47, 48].

The following clinical risk factors were associated with worst COVID-19 outcomes in CoCARE: ECOG PS ≥2, pre-existing co-morbidities, COVID-19 related symptoms, haematological malignancies and progressive disease. Although collectively these parameters are consistent

with those reported in other studies[17, 23, 32], intriguingly, we observed that overweight/obese patients (BMI≥25) experienced less often infection requiring hospitalization compared to patients with BMI<25. In other series, obesity has been associated with worse outcomes from COVID-19, in the general population[49-51] and cancer[17] , whereas this correlation was not confirmed by others[52]. Overweight status has been associated with better survival in patients with advanced cancer[53-55]. This so-called obesity paradox may be justified by increased treatment tolerability and fitness status associated with higher BMI[53]. Additionally, any correlation between obesity and clinical outcomes may be confounded by tumour characteristics and treatment (i.e., hormonotherapy)[53, 54]; although we found no such association between obesity and confounders in our cohort, except for a higher prevalence of obesity in patients with colorectal and breast cancers (Table S5). Finally, the correlation between BMI and cancer outcomes can be impacted by inaccurate or evolving over time BMI measurements. Moreover, adiposity and muscle mass contribute to BMI, are more potent prognosticators and can vary from patient to patient [53, 56, 57]. Further studies are needed to better assess the influence of BMI, muscle mass and adiposity for patients with cancer and COVID-19.

In our multivariable analysis, no significant association was found between current administration of cancer treatment and COVID-19 related outcomes. Although in some studies cytotoxic chemotherapy was associated with worse outcomes[28, 58], that was not confirmed in other cohorts[23, 32, 59]. Heterogeneity related to the class of therapies, treatment intention (curative vs non-curative), time between treatment and COVID-19 diagnosis and type of disease may contribute to these apparently contradictory results. Hormonotherapy, targeted therapy or immune checkpoint inhibitors have not been associated with worse outcomes from COVID-19 in recent literature[28, 32, 58, 60].

We independently validated NLR ≥ 6 and OIS ≤ 40 as prognosticators for COVID-19 severity and OIS ≤ 40 (at 10% significance level) for OS, following a previous publication by Dettorre et al[61, 62]. Systemic inflammatory response and several alterations in inflammation-related parameters have been associated with worst COVID-19 outcomes in the overall population[63-65] and also, in patients with cancer[28, 61, 66]. The NLR and OIS (or prognostic nutritional index) combine commonly used laboratory parameters (neutrophils, lymphocytes and albumin level), and represent easily accessible, inexpensive and valid scores that can be implemented in daily clinical practice. Among other available prognosticator algorithms, CORONET is a decision-support online tool focused on hospital admissions and recovery of patients with cancer and COVID-19[67 68], that has been updated integrating the ESMO-CoCARE data[69].

There are limitations from our study. This is an observational registry, with potential selection bias including missing values, the tendency to identify and report mainly the more severe cases, heterogeneity in patient management and data collection across institutions. We observed some differences in type and quality of data collected over time, in line with the increasing clinical experience and knowledge in managing patients with COVID-19. Finally, the

quality of data depended on each center, without the implementation of a centralized audit system. Despite these limitations, a unique electronic case report form (eCRF), as well as the multicenter, multi-country nature of the study with > 1500 cases included, empower a robust statistical analysis partly mitigating the selection bias.

In conclusion, in our study, male gender, older age, smokers, non-Asian ethnicity, poor ECOG PS, lower BMI, presence of co-morbidities, symptomatic COVID-19, higher NLR, lower OIS, haematological malignancies, more advanced disease stage and progressive cancer status were identified as risk factors for COVID-19 adverse outcomes in patients with cancer. We are now facing another phase of the pandemic with a significant proportion of patients with cancer vaccinated against COVID-19 across countries, many already receiving a vaccination boost, and new SARS-COV-2 variants of concern with different transmissibility and morbidity rates. In this rapidly evolving context, ESMO-CoCARE is committed to strengthen a worldwide network tackling unmet needs for people with cancer and COVID-19 with the long-term goal to support clinicians and regulatory bodies on the optimal management of patients with cancer.

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***Note**: Percentages represent presence of complications within each characteristic's category.*
ECOG: Eastern Cooperative Oncology Group, BMI: Body Mass Index

Table S7b. Association of most frequent type of complications during COVID-19 (pulmonary, cardiovascular, systemic) with co-morbidities
(*) Fisher's exact test for each type of complication separately, excluding 'Unknown/Missing'
***Note**: Percentages represent presence of complications within each characteristic's category.*

Table S7c. Association of most frequent type of complications during COVID-19 (pulmonary, cardiovascular, systemic) with cancer disease characteristics
(*) Fisher's exact test for each type of complication separately, excluding 'Unknown/Missing', (~) Excluding 'Not applicable'
***Note**: Percentages represent presence of complications within each characteristic's category.*
NED: No Evidence of Disease

Table S8. Detailed information on treatments for COVID-19 or its sequelae
(*) The same patient may have received more than one type of treatment

Table S9. Inflammatory-based biomarkers measured prior to COVID-19 diagnosis
***Note**: Inflammatory-based biomarkers were calculated based on the available laboratory measurements (prior COVID-19). These biomarkers have been introduced and analysed in the frame of OnCovid project (Dettorre, 2021). These cut-offs were used in the OnCovid project for positioning patients into good versus poor risk groups with respect to survival. The asterisk (*) refers to those groups with poor risk.*

Table S10a. Univariable associations of variables of interest with COVID-19 severity & recovery
(§) Out of the 1626 patients, 74 had 'Missing/Not applicable' severity status and 69 had 'Missing/Not applicable' recovery status, (*) Fisher's exact test excluding categories 'Unknown/Missing', ($) Odds of hospitalized patients (severe/moderate disease) versus non-hospitalized (mild disease), (#) Odds of recovered patients versus non-recovered, (&) Including African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Maori and other, (**) Low-income economies have a GNI per capita ≤ $1,045; lower middle-income are between $1,046 and $4,095; upper middle-income are between $4,096 and $12,695; high-income are those with ≥ $12,696 (World Bank Atlas 2020), (^) Comparison of 'NED' vs 'Active disease [CR/PR/SD/PD]', (@) Comparison of ' NED/CR' vs 'PR/SD/PD', (!) Comparison of 'PD' vs ' NED/CR/PR/SD'
ECOG: Eastern Cooperative Oncology Group, BMI: Body Mass Index, NED: No Evidence of Disease

Table S10b. Univariable associations of variables of interest with COVID-19 recovery, among hospitalized patients
(§) Out of the 990 hospitalized patients, 6 had 'Missing/Not applicable' recovery status, (*) Fisher's exact test excluding categories 'Unknown/Missing', (#) Odds of recovered patients versus non-recovered, (&) Including African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Maori and other, (**) Low-income economies have a GNI per capita ≤ $1,045; lower middle-income are between $1,046 and $4,095; upper middle-income are between $4,096 and $12,695; high-income are those with ≥ $12,696 (World Bank Atlas 2020), (^) Comparison of 'NED' vs 'Active disease [CR/PR/SD/PD]', (@) Comparison of ' NED/CR' vs 'PR/SD/PD', (!) Comparison of 'PD' vs ' NED/CR/PR/SD'

Table S10c. Univariable associations of variables of interest with Overall Survival
(§) Out of the 1626 patients, 414 had non-available follow-up information, (*) Log-rank test and Hazard ratio (95%) excluding categories 'Unknown/Missing', (&) Including African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Maori and other, (**) Low-income economies have a GNI per capita ≤ $1,045; lower middle-income are between $1,046 and $4,095; upper middle-income are between $4,096 and $12,695; high-income are those with ≥ $12,696 (World Bank Atlas 2020), (^) Comparison of 'NED' vs 'Active disease [CR/PR/SD/PD]', (@) Comparison of ' NED/CR' vs 'PR/SD/PD', (!) Comparison of 'PD' vs ' NED/CR/PR/SD'

ECOG: Eastern Cooperative Oncology Group, BMI: Body Mass Index, NED: No Evidence of Disease, NE: Non-Estimable

Table S11. Association between COVID-19 severity and recovery (N=1544)

Table S12. Causes of death (380 deaths among the 1212 patients of the OS analysis)
PD: Disease Progression
(*): In the frame of OS analysis, the total of 297 COVID-19 related deaths consisted of 296 patients reported as having not recovered from COVID-19 and 1 patient reported as recovered who died later during follow-up due to COVID-19 complications. Of note, in total, 304 patients were reported as having not recovered but for 8 of them death date was not provided and thus they were not included in the OS analysis.

Table S13. Other Investigators/ Collaborating Centers

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Figure S1. Distribution of patients diagnosed with COVID-19 across time (N=1626)
Note: *Two patients were diagnosed with COVID-19 in January 2020 and one in February 2020.*

Figure S2. Map of participating countries

Figure S3. Laboratory measurements over time (prior to COVID-19, during COVID-19 and at recovery)
Note*: Prior to COVID-19: prior measurement closest to COVID-19 diagnosis; during COVID-19: at 1 week after diagnosis or at severe worsening of the disease.*

COVID-19 and cancer: first report of the ESMO international, registry-based, cohort study (ESMO CoCARE)

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***Table 1**. Cohort demographics, clinical and cancer disease characteristics (N=1626)*

(*) Including African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Maori and other

Characteristic	**All patients (N=1626)**
Demographics	
Gender - n (%)	
Female	845 (52.0)
Male	757 (46.6)
Unknown/Missing	24 (1.5)
Age (years at COVID-19 diagnosis) - n (%)	
≤49	303 (18.6)
50-69	735 (45.2)
≥70	563 (34.6)
Unknown/Missing	25 (1.5)
Median (Q1-Q3)	*64 (53 - 73)*
Ethnicity - n (%)	
Caucasian	942 (57.9)
Non-Caucasian	466 (28.7)
Asian	117 (7.2)
Other*	349 (21.5)
Unknown/Missing	218 (13.4)
ECOG performance status - n (%)	
0	342 (21.0)
1	758 (46.6)
2	273 (16.8)
≥3	114 (7.0)
Unknown/Missing	139 (8.5)
Smoking history - n (%)	
Current smoker	148 (9.1)
Former smoker	373 (22.9)
Never smoker	658 (40.5)
Unknown/Missing	447 (27.5)
BMI (kg/m²) - n (%)	
Underweight (< 18.5)	57 (3.5)
Normal (18.5 ≤ BMI < 25)	490 (30.1)

Characteristic	All patients (N=1626)
Overweight (25 ≤ BMI < 30)	502 (30.9)
Obesity (≥ 30)	280 (17.2)
Unknown/Missing	297 (18.3)
Median (Q1-Q3)	*25 (22 - 29)*
Clinical characteristics	
Number of co-morbidities - n (%)	
0	447 (27.5)
1	510 (31.4)
>1	624 (38.4)
Unknown/Missing	45 (2.8)
Number of concomitant medications - n (%)	
0	501 (30.8)
≥1	956 (58.8)
Unknown/Missing	169 (10.4)
Cancer disease characteristics	
Date of cancer diagnosis - n (%)	
Within the past year	758 (46.6)
Within the past 5 years	552 (33.9)
More than 5 years ago	210 (12.9)
Unknown/Missing	106 (6.5)
Primary tumor type - n (%)	
Breast	332 (20.4)
Colorectal	234 (14.4)
Lung	221 (13.6)
Other solid tumor	619 (38.1)
Haematological malignancy	151 (9.3)
Unknown/Missing	69 (4.2)
Cancer status at COVID-19 diagnosis - n (%)	
Active disease, Complete response (CR)	56 (3.4)
Active disease, Partial response (PR)	129 (7.9)
Active disease, Stable disease (SD)	519 (31.9)
Active disease, Progressive disease (PD)	368 (22.6)
NED	335 (20.6)

Characteristic	All patients (N=1626)
Unknown/Missing	219 (13.5)
Cancer stage at COVID-19 diagnosis - n (%)	
I	65 (4.0)
II	162 (10.0)
III	242 (14.9)
IV	688 (42.3)
Not applicable	395 (24.3)
Unknown/Missing	74 (4.6)
On anti-cancer treatment at COVID-19 diagnosis - n (%)	
Yes (up to 3 months prior to COVID-19 diagnosis)	1053 (64.8)
No	424 (26.1)
Unknown/Missing	149 (9.2)
Past systemic treatment - n (%)	
Yes	707 (43.5)
No	661 (40.7)
Unknown/Missing	258 (15.9)

***Note**: The 'Not applicable' cancer stage category includes cases for which cancer stage could not be determined: due to patient's cancer type or because cancer re-staging was not available.*
ECOG: Eastern Cooperative Oncology Group, BMI: Body Mass Index, NED: No Evidence of Disease

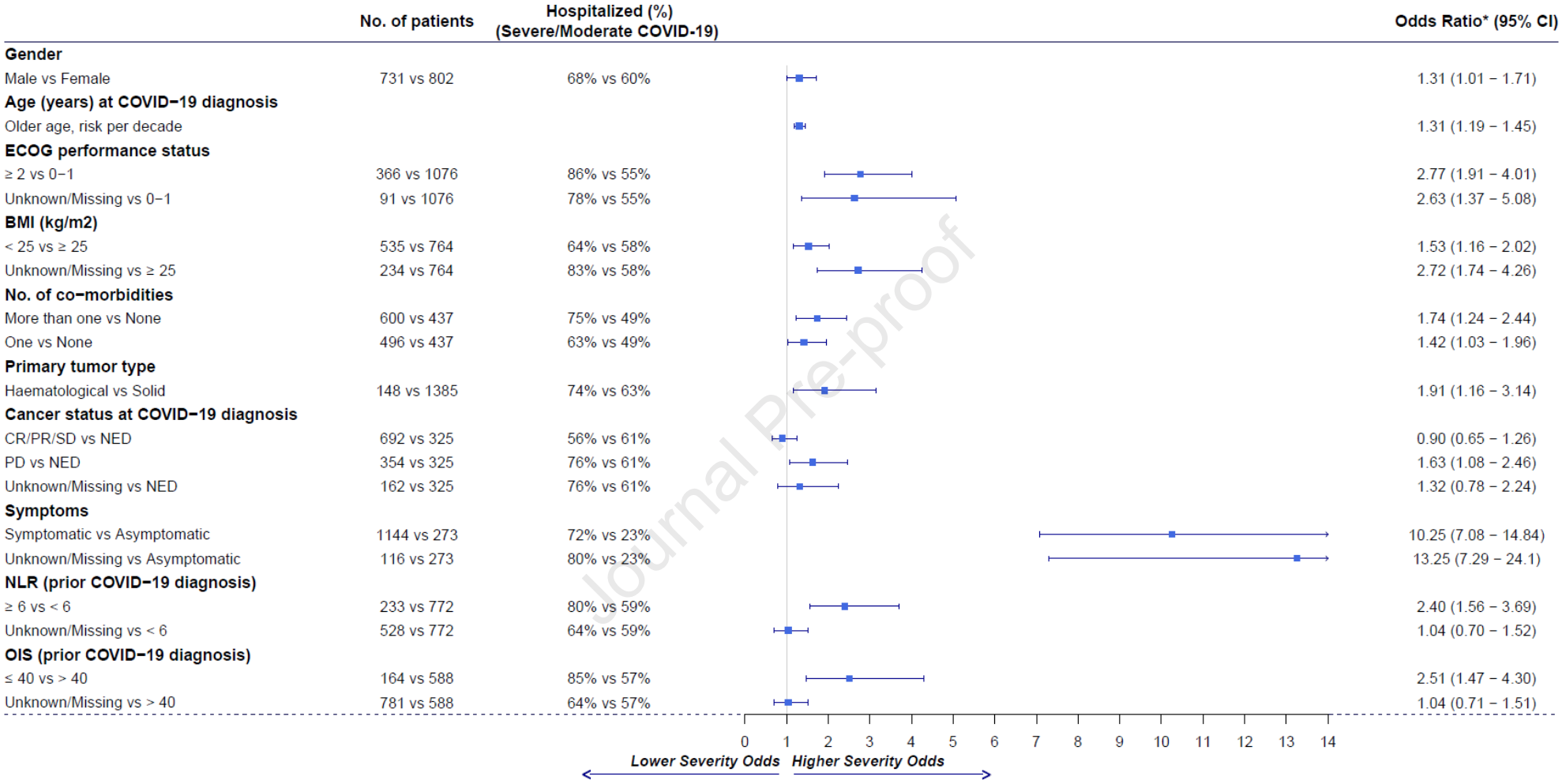
***Table 2**. COVID-19 diagnosis, course of illness and recovery (N=1626)*

Characteristic	All patients (N=1626)
COVID-19 suspection confirmed with laboratory tests - n (%)	
RT-PCR	1050 (64.6)
SARS-CoV-2 Serology	126 (7.7)
Serum Ig, Ig subtypes	21 (1.3)
Other *(blood cultures/swab/vector-best system)*	31 (1.9)
Not confirmed	175 (10.8)
Unknown/Missing	223 (13.7)
Symptoms - n (%)	
Yes (symptomatic)	1167 (71.8)
Fever (>38° C)	797 (49.0)
Cough (incl. productive cough)	745 (45.8)
Dyspnea	542 (33.3)
Severe fatigue	333 (20.5)
Myalgia	218 (13.4)
Headache	185 (11.4)
Other (incl. symptoms experienced by <10% of the patients)	638 (39.2)
No (asymptomatic)	280 (17.2)
Unknown/Missing	179 (11.0)
Primary endpoint: Severity of COVID-19 illness - n (% excluding 'Unknown/Missing')	
Mild [no hospitalization took place]	562 (36.2)
Moderate [hospitalization took place or indicated, but no ICU]	822 (53.0)
Severe [ICU admission or at least indication]	168 (10.8)
Unknown/Missing	74
Complications occurring during COVID-19 - n (%)	
At least one	641 (39.4)
Pulmonary	477 (29.3)
Cardiovascular	182 (11.2)
Systemic	156 (9.6)
Gastrointestinal	86 (5.3)
Other	260 (16.0)
None	917 (56.4)
Unknown/Missing	68 (4.2)
Requirement of oxygen during the illness - n (%)	

Characteristic	All patients (N=1626)
Yes	609 (37.5)
No	821 (50.5)
Unknown/Missing	196 (12.1)
Receipt of any treatment for COVID-19 or its sequelae - n (%)	
Yes	795 (48.9)
No	819 (50.4)
Unknown/Missing	12 (0.7)
Primary endpoint: Recovery from COVID-19 - n (% excluding 'Unknown/Missing')	
Yes	1253 (80.5)
No (COVID-19 death*)	304 (19.5)
Unknown/Missing	69
Primary endpoint: Overall Survival status - n (% excluding 'Unknown/Missing')	
Alive (at last follow-up)	832 (68.6)
Dead (with death date available)	380 (31.4)
Unknown/Missing (non-available follow-up)	414

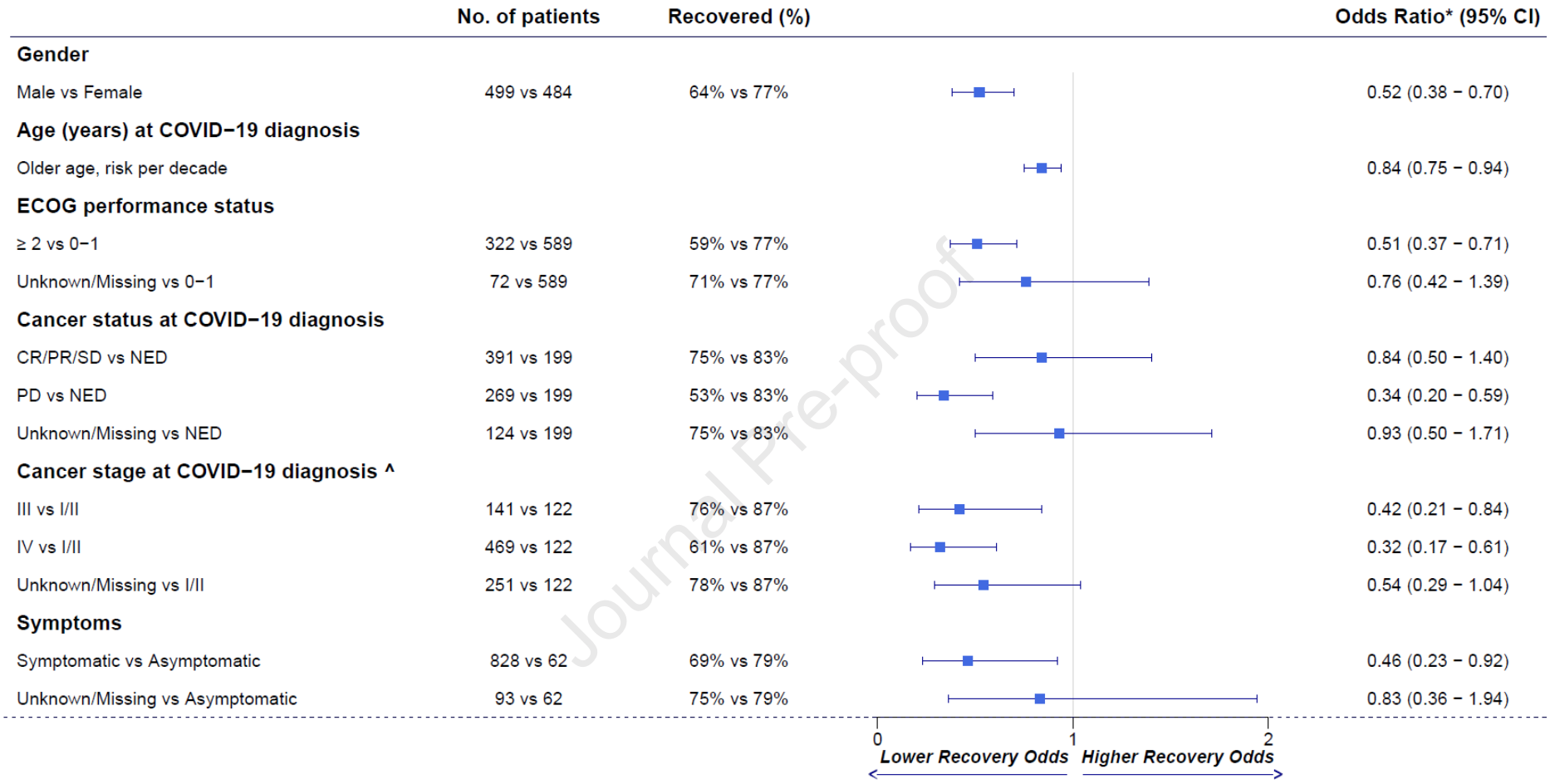
***Note**: A detailed table with all symptoms is provided in the supplement (Table S6a).*
(*): Death date was not reported for 8 of the 304 patients that did not recover from COVID-19RT-PCR: Reverse Transcription - Polymerase Chain Reaction, Ig: Immunoglobulin

***Figure 1a**. Multivariable logistic model for COVID-19 severity*



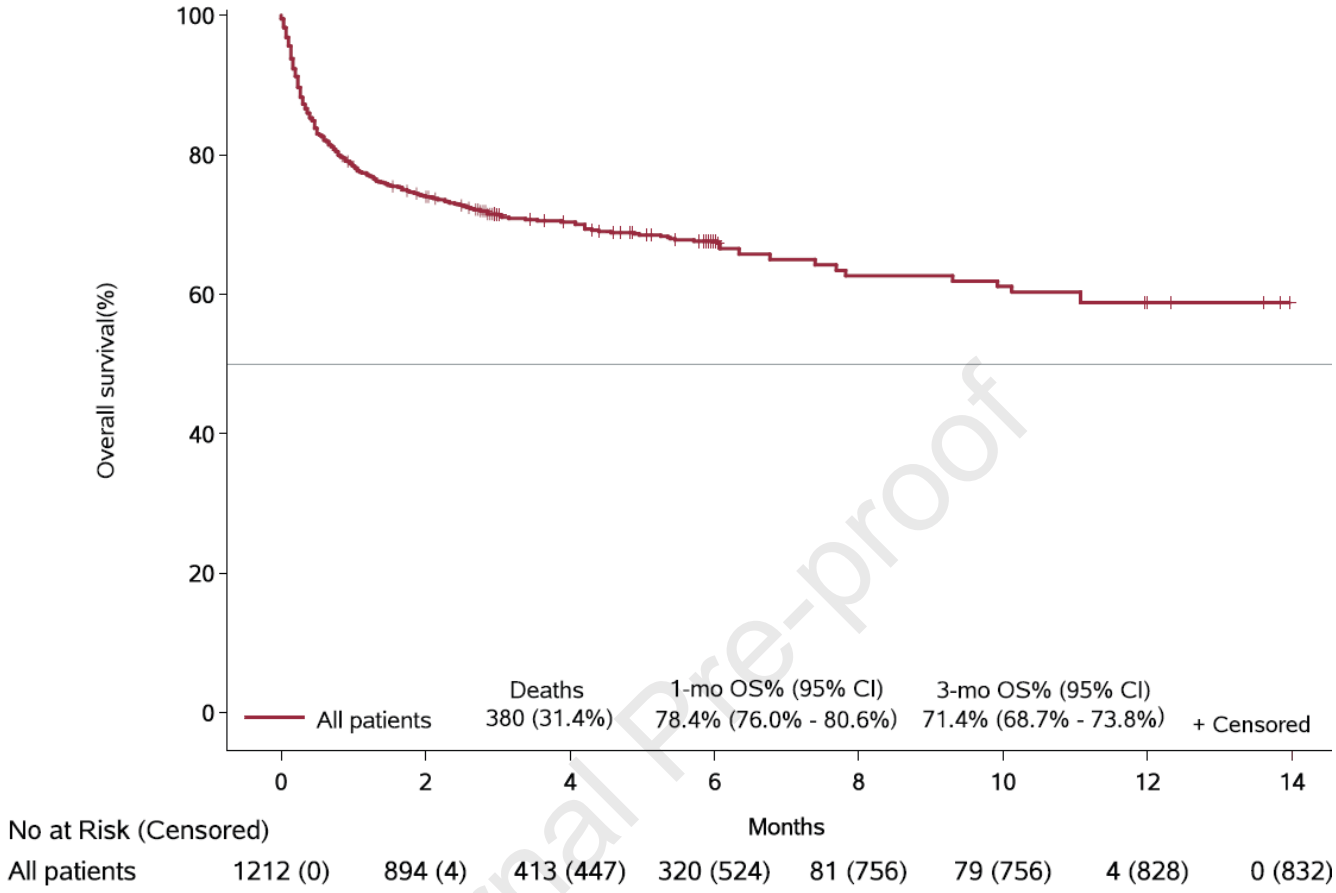
(*) Odds Ratios (95% CI) for Hospitalized (Severe/Moderate disease) vs. Non-hospitalized (Mild disease).
***Note**: The model was based on 1533 patients, including 976 patients with Hospitalization (Severe/Moderate COVID-19).*

***Figure 1b**. Multivariable logistic model for COVID-19 recovery, including only patients with hospitalization (severe/moderate COVID-19 disease)*



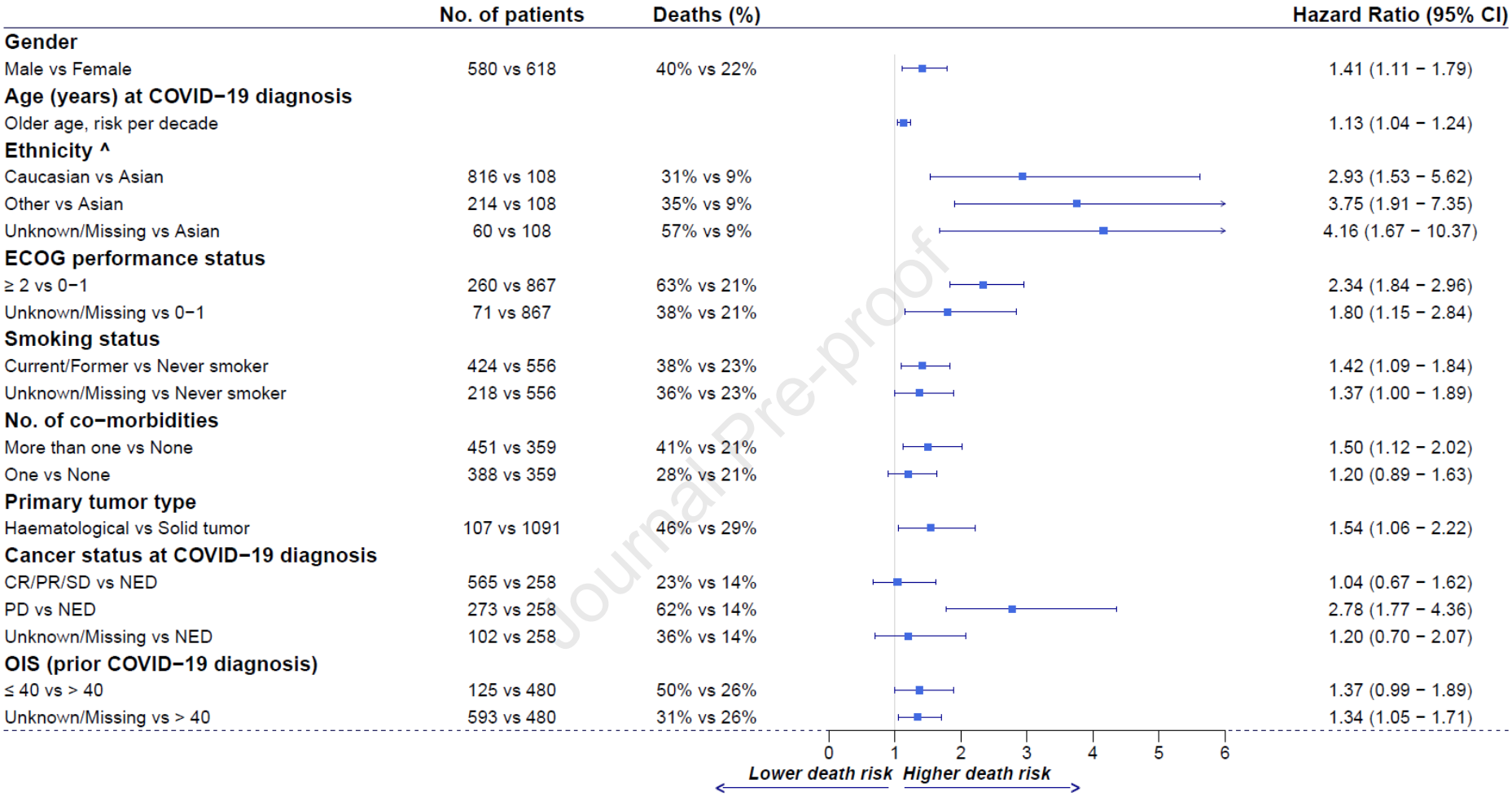
(*) Odds Ratios (95% CI) for Recovered vs. Non-recovered.
(^) 'Not applicable' category is also included in the 'Unknown/Missing' category.
***Note**: Among patients with available recovery information, 984 patients needed hospitalization. However, the model was based on 983 hospitalized patients (severe/moderate COVID-19), including 694 recovered patients, since there was 1 patient with missing age.*

***Figure 2a**. Overall Survival (N=1212)*



***Note**: Only patients with available follow-up information are included.*

***Figure 2b**. Multivariable Cox model for Overall Survival (stratified by cancer stage at COVID-19 diagnosis and symptoms)*



(^) In 'Other' category: African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Maori and other are included.
The respective hazard ratio (95% CI) for 'Other' vs 'Caucasian' is 1.28 (0.96 - 1.69).
***Note 1**: The model was based on 1198 patients, including 370 deaths.*
***Note 2**: Cancer stage at COVID-19 diagnosis and symptoms were used as stratification factors due to violation of the proportionality hazard assumption.*